Chemical perturbation of an intrinsically disordered region of TFIID distinguishes two modes of transcription initiation.

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Public Summary:
Intrinsically disordered proteins/regions (IDPs/IDRs) are proteins or peptide segments that fail to form stable 3-dimensional structures in the absence of partner proteins. They are abundant in eukaryotic proteomes and are often associated with human diseases, but their biological functions have been elusive to study. In this study, we report the identification of a tin(IV) oxochloride-derived cluster that binds an evolutionarily conserved IDR within the metazoan TFIID transcription complex. Binding arrests an isomerization of promoter-bound TFIID that is required for the engagement of Pol II during the first (de novo) round of transcription initiation. However, the specific chemical probe does not affect reinitiation, which requires the re-entry of Pol II, thus, mechanistically distinguishing these two modes of transcription initiation. This work also suggests a new avenue for targeting the elusive IDRs by harnessing certain features of metal-based complexes for mechanistic studies, and for the development of novel pharmaceutical interventions.

Scientific Abstract:
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